INFLUENCE OF DEXTRO-THYROXINE AND ANDROSTERONE ON BLOOD CLOTTING FACTORS AND SERUM CHOLESTEROL IN PATIENTS WITH ATHEROSCLEROSIS*

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STUDIES WITH dextro-thyroxine during the last six years have demonstrated that this agent exerts a significant hypocholesterolemic effect with little or no change in the metabolic rate, pulse, and electrocardiographic findings.[1, 2] In 1959, Gallagher and his co-workers[3] demonstrated that administration of tri-iodothyronine increases the excretion of androsterone and etiocholanolone, modifies their urinary ratio and decreases serum cholesterol in patients with hypothyroid and idiopathic hypercholesterolemia. They also showed that intramuscular administration of androsterone lowers serum cholesterol concentration.

Other investigators have shown an increase in *in vitro* blood coagulability during alimentary lipemia[4] and an increased coagulability in atherosclerotic subjects.[5] In addition, blood coagulation has been reported to be increased in hypothyroid and decreased in hyperthyroid conditions.[6] The effect of an anti-coagulant of the dicumarol type on the prothrombin time has been found to be significantly increased in hyperthyroid rabbits and markedly decreased in hypothyroid rabbits.[7] Some evidence has also been presented that coronary atherosclerotic patients have an increased concentration of antihemophilic globulin.[8]

An increase in cephalins in plasma and red cells in atherosclerotic patients was recently demonstrated,[9] and a fall in phospholipids and β-lipoprotein levels was noted in patients receiving dextro-thyroxine.[10]

Several workers have shown that phosphatidyl ethanolamine promotes clotting,[11-14] while phosphatidyl serine either is inactive or exerts an anti-coagulant effect.[13-15]

This paper describes our studies on the effects of the administration of oral dextro-thyroxine and intramuscular androsterone on serum cholesterol, blood coagulation factors, and urinary excretion of androsterone and etiocholanolone of patients with atherosclerosis.

MATERIAL AND METHODS

Thirty-one patients were studied: 13 were men and 18 women. Their ages ranged from 17 to 71 years with an average of 52 years. All female subjects were in their postmenopausal period with the exception of three in whom the tests were performed in the middle of the menstrual cycle.

All patients, with the exception of a 17-year-old girl with a nephrotic syndrome, were atherosclerotic as judged by the following criteria: personal or familial history (peripheral vascular disease, myocardial ischemia, cerebral thrombosis); physical examination (aortic-systolic murmur, retinal artery changes in fundi, palpation of arteries); electrocardiographic signs of coronary ischemia and radiological evidence of dilatation of the aorta with or without calcification. The basal metabolic rate, protein-bound iodine and radioactive iodine^{131} uptake tests were performed in myxedematous patients. Milky or lactescent serum and an increase in serum neutral fats (triglycerides) were the criteria of hyperlipemia. During the study, a group of patients were on a low saturated fat diet* with added corn oil (60 c.c./day), and another group received a fixed diet containing 50% of carbohydrates, 30% of lipids and 20% of proteins.

Twenty-three patients received oral dextro-thyroxine and were arbitrarily divided into four groups.

Group A: Patients with serum cholesterol levels below 250 mg. %: 3

Group B: Patients with serum cholesterol levels above 250 mg. %. 13

Group C: Myxedematous patients: 5

Group D: Myxedematous patients: 2. These patients received thyroid extract (Parke Davis) in a mean dosage of 15 mg./day for six weeks and were used as controls for comparison with patients of group C.

The mean dosage of dextro-thyroxine was 4 to 6 mg./day for a mean duration of 13 weeks, higher dose levels being used for patients with previously untreated spontaneous hypothyroidism.

Eight patients received intramuscular androsterone in a mean dosage of 100 mg./day for 10 days and were similarly divided into three groups:

Group A: Patients with serum cholesterol below 250 mg. %: 4.

Group B: Patients with serum cholesterol above 250 mg. %: 3.

Group C: Myxedematous patient: 1.

The parameters studied were:

A. Blood coagulation: (1) Platelet clumping time (viscous metamorphosis); (2) platelet adhesive index; (3) thromboplastin generation tests: (i) $Al(OH)_3$-treated plasma; this test is a measure of both Factors V (accelerator-globulin) and VIII (antihemophilic globulin or AHG); (ii) Factor IX (Christmas factor or plasma thromboplastin component, PTC) on plasma; (iii) Factor IX (Christmas

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*A diet excluding egg yolk and dairy products such as butter, whole milk, cream, yoghurt, cheese and ice cream; also mayonnaise, spreads containing meat fat, chocolate and meat fats. Meal containing very lean meat (veal, beef, chicken or turkey) was permitted once a day. Fish was permitted *ad libitum*.

factor or plasma thromboplastin component, PTC) on serum; (iv) Platelet activity.

B. Serum cholesterol.

C. Urinary androsterone and etiocholanolone.

From each subject, 50 ml. of blood was collected with a paraffin-coated glass syringe and an 18-gauge stainless-steel needle. Ten ml. of blood was placed in a silicone*-coated glass centrifuge tube at 4° C. This sample was used for determining the platelet clumping time (macroscopic method). Nine ml. of blood was placed in a silicone-coated centrifuge tube in the proportion of nine parts of blood to one part of 3.8% trisodium citrate. This sample was used for the platelet adhesive index (glass wool filter method of Moolten and Vroman),[16] and thromboplastin generation test (method of Biggs and Douglas,[17] modified by Mustard).[18] Serum (non-citrated plasma incubated at 37° C. for five hours) obtained from the remaining blood was used for factor IX and cholesterol determinations.

The method of Abell and co-workers[19] was used for determining serum cholesterol concentration.

For the determination of urinary androsterone and etiocholanolone, a 4- to 6-hour aliquot of complete 24-hour urine collection was used. Urine was extracted with chloroform following incubation with animal β-glucuronidase (300 units per ml. of urine) at pH 4.8 for 72 hours at 37° C. After readjustment to pH 1 with 0.25 H_2SO_4, incubation at room temperature (25° C.) was allowed to proceed for 48 hours. Two additional chloroform extractions were performed at the end of each 24-hour period. After extensive washings of these pooled extracts with 0.1 N NaOH and distilled water, and re-extraction of these washings with $HCCl_3$, the pooled chloroform extracts were dried over 2 g. of anhydrous sodium sulfate per 100 ml. of chloroform extract. These chloroform extracts were evaporated to dryness in a rotary type evaporator* at less than 45° C.

The individual steroids were separated in the Kochakian[20] paper chromatographic system (benzene-cyclohexane (1:1)/propylene glycol-methanol (1:1)), and were located by spraying a strip 0.5 cm. wide with alkaline m-dinitrobenzene solution, a solution of 3 vol. of 2% meta-dinitrobenzene and of 2 vol. of 2.5 N KOH, prepared just before use. The areas corresponding to the standards androsterone and etiocholanolone were eluted with ethanol. The residues from these eluates were dissolved in benzene and chromatographed on an aluminium oxide column (7 x 0.7 cm.). The successive eluents used in amounts of 100 ml. each were: (1) benzene, (2) benzene–0.1% ethanol, (3) benzene–0.5% ethanol. The last eluent was evaporated and the absorption at 515 μ and at 420 μ, after reaction with alkaline m-dinitrobenzene and with the Allen's correction, was measured on a Beckman model DU spectrophotometer.[21, 22]

TABLE I.—DEXTRO-THYROXINE STUDIES (23 PATIENTS)

Groups	No. pts.	Mean serum cholesterol (mg. %)			Index of adhesiveness			Platelets clumping time (sec.)		
		Controls (2)	4-6 mg./day for 13 wk.	% change	Controls (2)	4-6 mg./day for 13 wk.	% change	Controls (2)	4-6 mg./day for 13 wk.	% change
A	3	233 S.E. ±8.5	186† S.E. ±7	−21	1.37 S.E. ±0.05	1.05† S.E. ±0.04	−24	142 S.E. ±19	198* S.E. ±15	+39
B	13	363 S.E. ±19.4	300* S.E. ±15.8	−19	1.34 S.E. ±0.03	1.09† S.E. ±0.016	−19	135 S.E. ±6.7	179† S.E. ±6.0	+32
C	5	412 S.E. ±7.5	234† S.E. ±11.1	−44	1.44 S.E. ±0.06	1.17† S.E. +0.02	−19	134 S.E. ±12.2	204† S.E. ±5.1	+52
D	2	400 S.E. ±54	307 S.E. ±45	−24	1.5 S.E. ±0.14	1.16* S.E. ±0.04	−23	148 S.E. ±30	171 S.E. ±20	+15

Group A: Patients with serum cholesterol below 250 mg. % (3).
Group B: Patients with serum cholesterol above 250 mg. % (13).
Group C: Myxedematous patients (5).
Group D: Myxedematous patients (2).
Thyroid extract (P.D.) mean dosage: 15 mg./day for 6 weeks.

*Difference between control and treated is significant at $.05 \geq p > .01$
†Difference between control and treated is significant at $p \leq .01$

RESULTS

A. *Dextro-thyroxine Studies*

The detailed results obtained from groups receiving dextro-thyroxine are shown in Table I. The main findings are: a fall from the average pre-treatment serum cholesterol of 21%, 19% and 44% in groups A, B and C, respectively; a decrease in platelet adhesive index of 24% in group A, and of 19% in groups B and C; a prolongation in platelet clumping time of 39%, 32% and 52% in groups A, B and C, respectively. The changes in the thromboplastin generation test are indicated in Table II.

A slight but significant decrease in the activity of the $Al(OH)_3$-treated plasma, and of factor IX (PTC or Christmas factor) on serum and plasma

*Dri Film SC-87, General Electric Co.

*Flash evaporator, Laboratory Glass Supply Co., New York 31, N.Y.

TABLE II.—DEXTRO-THYROXINE STUDIES (23 PATIENTS)

Thromboplastin generation test	*Incubation time in min.*	*Group A (3 patients)*				*Group B (13 patients)*				*Group C (5 patients)*				*Group D (2 patients)*			
Activity		*Controls (2) S.E.*		*4-6 mg./day S.E. for 13 wk.*		*Controls (2) S.E.*		*4-6 mg./day S.E. for 13 wk.*		*Controls (2) S.E.*		*4-6 mg./day S.E. for 13 wk.*		*Controls (2) S.E.*		*15 mg./day S.E. for 6 wk.*	
$Al(OH)_3$	1	42.83	±0.7	48.78†	±1.8	44.32	±0.6	47.91†	±0.78	42.56	±1.6	47.00*	±0.60	40.60	±2.9	49.62	±2.5
Treated plasma	2	17.50	±1.1	19.60*	±0.6	16.80	±0.47	18.98†	±0.40	16.91	±1.5	19.41	±0.52	17.87	±2.4	19.04	±0.9
Clotting time	3	11.00	±0.6	12.40*	±0.1	11.39	±0.29	12.27*	±0.18	11.31	±0.5	12.58*	±0.18	10.50	±0.3	13.10	±0.8
(seconds)	4	9.83	±0.3	11.87†	±0.2	10.50	±0.15	11.86†	±0.17	10.56	±0.4	11.88*	±0.16	10.62	±0.3	12.35	±0.4
SERUM	1	40.66	±1.0	44.52†	±0.8	40.50	±0.98	43.78*	±0.52	38.00	±2.0	43.79*	±0.43	44.25	±5.0	43.29	±3.5
IX—P.T.C.	2	15.41	±0.5	18.14†	±0.7	16.36	±0.62	18.30*	±0.36	15.98	±0.7	19.18†	±0.51	15.00	±1.0	17.50	±2.0
Clotting time	3	11.16	±0.7	12.17	±1.0	11.38	±0.21	12.00*	±0.20	11.31	±0.6	12.45	±0.22	12.00	±0.6	12.46	±0.3
(seconds)	4	10.16	±0.2	11.81†	±0.2	10.40	±0.14	11.50†	±0.18	10.61	±0.3	12.14†	±0.24	11.37	±0.5	12.27	±0.17
PLASMA	1	49.50	±1.1	53.77*	±1.0	50.25	±0.72	54.21†	±0.55	51.76	±1.9	54.19	±0.69	49.75	±3.1	53.97	±1.8
IX—P.T.C.	2	20.33	±2.0	25.92*	±0.4	23.00	±0.38	25.19†	±0.40	23.33	±0.7	24.66	±0.49	21.25	±2.9	24.70	±0.9
Clotting time	3	12.75	±0.6	15.61*	±1.0	14.09	±0.20	14.94†	±0.14	13.88	±0.5	14.82	±0.24	14.00	±1.0	14.45	±0.6
(seconds)	4	12.33	±0.7	14.71†	±0.1	13.46	±0.19	14.56†	±0.14	12.96	±0.4	14.29*	±0.25	13.50	±0.8	13.97	±0.7
PLATELETS	1	45.33	±3.3	51.48	±1.0	49.26	±1.10	49.26	±0.87	45.76	±1.3	49.69*	±0.69	44.75	±4.9	50.06	±2.3
	2	22.75	±0.9	22.03	±0.7	22.69	±0.68	21.43	±0.84	21.76	±1.2	21.19	±0.39	21.62	±2.1	24.37	±1.9
Clotting time	3	16.50	±0.7	16.25	±1.4	16.90	±0.54	15.44*	±0.26	16.75	±0.5	15.78	±0.31	17.87	±1.0	16.73	±0.6
(seconds)	4	15.82	±0.8	14.77	±0.4	16.96	±0.39	14.94†	±0.25	16.56	±0.7	15.17	±0.30	17.62	±1.3	15.87	±0.4

GROUP A: Patients with serum cholesterol below 250 mg. % (3).
GROUP B: Patients with serum cholesterol above 250 mg. % (13).
GROUP C: Myxedematous patients (5).
GROUP D: Myxedematous patients (control): 2 patients with thyroid extract (P.D.).

* Difference between "control" and "treated patients" significant at $.01 < p \leq 0.05$.

†Difference between "control" and "treated patients" significant at $p \leq 0.05$.

is observed, as compared with the pre-treatment values. Presumably Hageman or other factors increase in activity during this phase, but we have as yet been unable to dissociate these changes from those of factor IX. In contrast, the platelets appeared more active with a shortening of clotting time.

Urinary androsterone and etiocholanolone were determined in three myxedematous patients. During the control period, the daily combined excretion of androsterone and etiocholanolone was 0.8, 0.1 and 1.1 mg. and increased to 4.0, 2.5 and 2.5 mg. after 60, 20 and 20 days on dextrothyroxine, respectively.

Statistical comparison of these groups has little value because of the marked differences in initial cholesterol levels, the small number of patients and the differences in age. Nevertheless, the fall in serum cholesterol and the prolongation of platelet clumping time expressed as per cent change from control values are more marked in myxedematous group C than in euthyroid groups A and B, although the platelet adhesive index did not show such a marked difference in all three groups.

In the thromboplastin generation test, at the third and fourth minute of incubation, the differences in clotting time between these groups were not significant. Usually, the changes in these tests first appeared two or four weeks after the beginning of therapy, with a peak at about the sixth or eighth week.

The trends of these various parameters before and during dextrothyroxine administration in these patients warrant illustration in individual cases.

Fig. 1 shows the changes in serum cholesterol, platelet adhesive index, platelet clumping time, clotting time of $Al(OH)_3$-treated plasma and of Factor IX (on serum at the fourth minute of incubation), in a 55-year-old man with a history of renal hypertension. Angiography revealed a narrowing due to an atheromatous plaque in the left renal artery. Moderate arteriosclerotic changes were seen on examination of the fundi and a systolic aortic murmur was heard on auscultation. The roent-

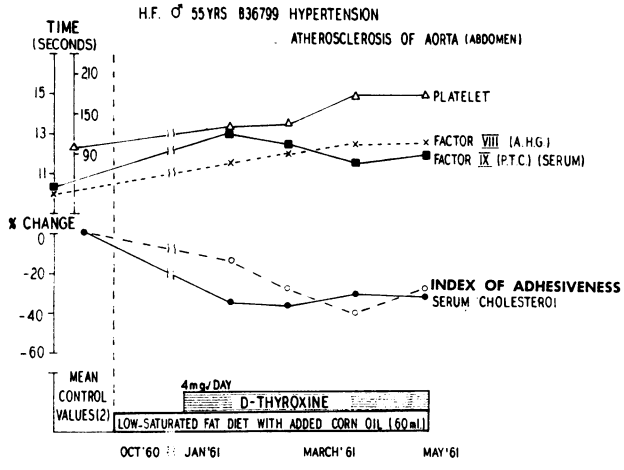

Fig. 1.—Effects of d-thyroxine given for four months at 4 mg./day to a hypertensive patient on platelet clumping time (△—△) expressed in seconds, $Al(OH)_3$-treated plasma (x- - -x) and factor IX (P.T.C. or Christmas) of serum (■—■) expressed in seconds at the fourth minute of incubation, index of adhesiveness (o- - -o) and serum cholesterol (●—●) expressed in per cent change from control values.

TABLE III.—PATIENT H.F., B36799, 55 YEARS OLD

Tests	*Average control values (2)*	*During treatment mean values (4) (18 weeks)*
Serum cholesterol	245 mg. %	168 mg. %
Platelet adhesive index	1.5	1.07
Platelet clumping time	97 sec.	154 sec.
At the fourth minute of incubation:		
(a) Activity of aluminum-treated plasma)	10 sec.	12.12 sec.
(b) Activity of Factor IX (P.T.C.) (measured on serum)	10.25 sec.	12 sec.
(c) Activity of Factor IX (P.T.C.) (measured on plasma)	10.75 sec.	15.4 sec.
(d) Activity of platelets	16.5 sec.	15.4 sec.

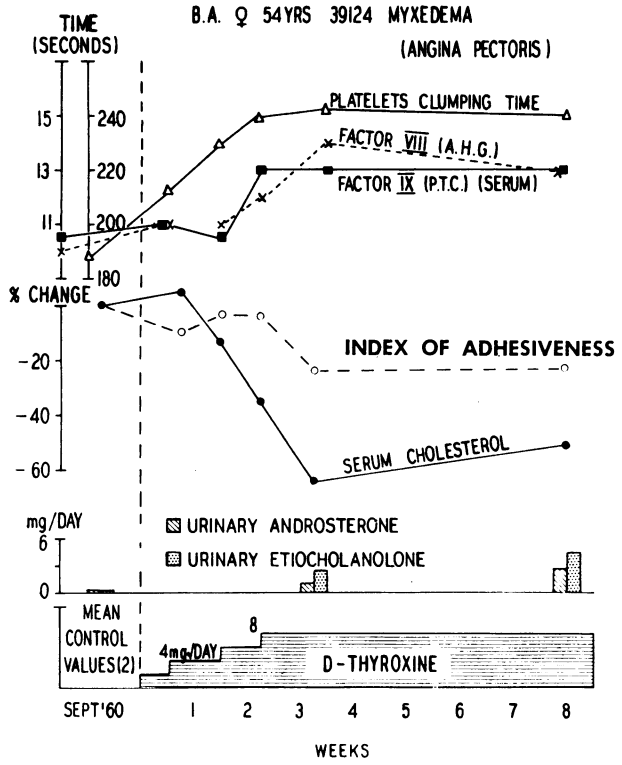

Fig. 2.—Effects of d-thyroxine given for eight weeks at a mean dosage of 6 mg./day to a myxedematous patient on the same parameters as in Fig. 1. Note that the legend is the same as that in Fig. 1.

genogram of the chest showed dilatation of the aorta with left ventricular hypertrophy. This patient received d-thyroxine for a period of four months at 4 mg./day. The detailed results are given in Table III.

Fig. 2 illustrates similar changes in a 54-year-old myxedematous woman, described in detail in Table IV. This patient had a history of myxedema of five years' duration: sensitivity to cold, puffiness of the face, eyelids and hands, and repeated attacks of angina pectoris and dyspnea on exertion. On physical examination, the speech was slow and the voice had a deep tone. Drowsiness, dry and thickened

TABLE IV.—PATIENT B.A., B39124, 54 YEARS OLD

Tests	*Average control values (2)*	*During treatment mean values (5) (8 weeks)*
Serum cholesterol	385 mg. %	261 mg. %
Platelet adhesive index	1.45	1.26
Platelet clumping time	188 sec.	232 sec.
At the fourth minute of incubation:		
(a) Activity of aluminum-treated plasma	10 sec.	12.2 sec.
(b) Activity of Factor IX (P.T.C.) (measured on serum)	10.5 sec.	12.1 sec.
(c) Activity of Factor IX (P.T.C.) (measured on plasma)	12 sec.	13 sec.
(d) Activity of platelets	18 sec.	16 sec.
Sum of urinary androsterone and etiocholanolone	0.8 mg./day	4.0 mg./day*

*Average of four 24-hour period values.

skin, and bradycardia at 60 beats per minute were also noted. Her basal metabolic rate was −25, radioactive iodine[131] uptake was 3.4% after 24 hours, and P.B.I. was 3.3 μg. %. After five weeks of administration of d-thyroxine, the anginal pains were less severe in intensity and frequency.

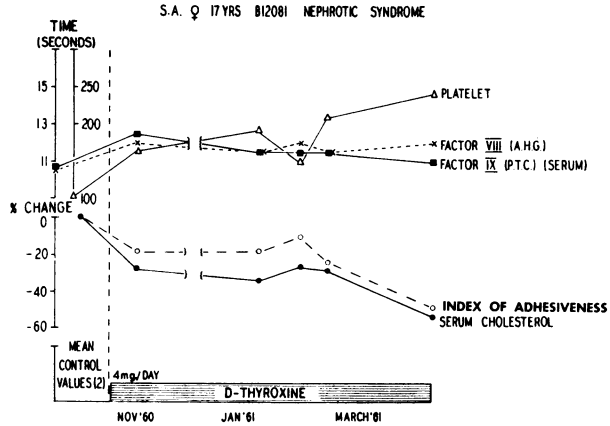

Fig. 3.—Effects of d-thyroxine given for six months at 4 mg./day to a 17-year-old girl with a nephrotic syndrome on the same parameters as in Fig. 1. Note that the legend is the same as that in Fig. 1.

The results obtained in a 17-year-old girl with a nephrotic syndrome are shown in Fig. 3. In this hypercholesterolemic patient, the trend of changes in serum cholesterol, platelet adhesive index, platelet clumping time and plasma thromboplastin time are the same as in atherosclerotic patients. The detailed results are given in Table V. After 24 weeks on dextro-thyroxine, serum neutral fats showed a significant decrease.

TABLE V.—PATIENT S.A., B12081, 17 YEARS OLD

Tests	*Average control values (2)*	*During treatment mean values (5) (24 weeks)*
Serum cholesterol	674 mg. %	457 mg. %
Platelet adhesive index	1.45	1.15
Platelet clumping time	100 sec.	192 sec.
At the fourth minute of incubation:		
(a) Activity of aluminum-treated plasma	10.5 sec.	11.8 sec.
(b) Activity of Factor IX (P.T.C.) (measured on serum)	10.75 sec.	11.6 sec.
(c) Activity of Factor IX (P.T.C.) (measured on plasma)	13.75 sec.	14 sec.
(d) Activity of platelets	18.5 sec.	15 sec.

Clinical Effects

Hypothyroid and euthyroid patients treated with dextro-thyroxine reported an increased sense of well-being two to four weeks after the beginning of therapy. Three myxedematous patients showed a rapid loss of weight and decrease in asthenia.

One hypothyroid and five euthyroid patients observed a reduction in intensity and frequency of anginal attacks. One subject suffering from angina

TABLE VI.—ANDROSTERONE STUDIES (8 PATIENTS)

Groups	No. pts.	Mean serum cholesterol (mg. %)			Index of adhesiveness			Platelet clumping time (sec.)		
		Controls (2)	10 mg./day for 10 days	% change	Controls (2)	100 mg./day for 10 days	% change	Controls (2)	100 mg./day for 10 days	% change
A	4	187 S.E. ±9	159 S.E. ±14	−16	1.45 S.E. ±0.04	1.24* S.E. ±0.07	−15	144 S.E. ±7.5	182* S.E. ±14.0	+26
B	3	253 S.E. ±20	194* S.E. ±16	−24	1.43 S.E. ±0.07	1.28 S.E. ±0.07	−11	136 S.E. ±12	186† S.E. ±8.4	+36
C	1	521	346	−34	1.3	1.19	−9	127	210	+57

Group A: Patients with serum cholesterol below 250 mg. % (4).
Group B: Patients with serum cholesterol above 250 mg. % (3).
Group C: Myxedematous patient (1).

*Difference between control and treated is significant at $.05 \geq p > .01$
†Difference between control and treated is significant at $p \leq .01$

attacks manifested no clinical improvement with the medication.

No side effects were noted during this study. We observed no thyrotoxic effects, except in a euthyroid patient who received 12 mg. of dextro-thyroxine per day for 11 weeks and manifested nervousness, tremors and diaphoresis. No escape phenomena in the various tests occurred during the therapy.

For comparison, thyroid extract (Parke Davis) was given to two myxedematous patients with a daily mean dosage of 15 mg. for six weeks (Group D). Changes of the same degree and in the same direction were observed as in those patients treated with dextro-thyroxine administration.

The percentage of variations were −24%, −23% and +15% for serum cholesterol, platelet adhesive index and platelet clumping time, respectively. The thromboplastin generation test showed the same trends as in the dextro-thyroxine group.

B. *Androsterone Studies* (Table VI)

Androsterone administration resulted in a fall from average pretreatment serum cholesterol values of 16%, 24% and 34% for groups A, B and C, respectively. No significant difference in platelet adhesive index in the three groups was noted, but we observed a marked prolongation of platelet clumping time in group C as compared with that in groups A and B. Nevertheless, a statistical approach is quite difficult, because of the small number[8] of patients studied.

In the thromboplastin generation test, at the third and fourth minute of incubation, we noticed in all groups except group A, the same trend as in the dextro-thyroxine group (Table VII). In group A, the changes were not significant. These discrepancies may be explained by the fact that therapy had to be stopped in two of the four group A patients because the injections became too painful.

Fig. 4 illustrates the changes obtained in a 48-year-old euthyroid man suffering from repeated attacks of angina pectoris on exertion with dyspnea and sweating. This patient has a history of attacks of angina pectoris. Pain was promptly relieved by nitroglycerin. The physical examination showed moderate arteriosclerotic changes in fundi and a systolic aortic murmur. Dilatation of aorta was present on the teleroentgenogram of the heart. No improvement of angina occurred during medication. A significant fall in serum cholesterol, a decrease

TABLE VII.—ANDROSTERONE STUDIES (8 PATIENTS)

Thromboplastin generation test	Incubation time in min.	Group A (4 patients)				Group B (3 patients)				Group C (1 patient)			
Activity		Controls (2)	S.E.	100 mg./day for 10 days	S.E.	Controls (2)	S.E.	100 mg./day for 10 days	S.E.	Controls (2)	S.E.	100 mg./day for 10 days	S.E.
$Al(OH)_3$ treated plasma clotting time (sec.)	1	45.75	±2.1	45.50	±2.2	39.58	±3.6	45.43	±1.6	53.00		46.30*	
	2	18.12	±0.6	19.37	±1.0	15.50	±1.2	18.68*	±0.8	17.50		23.00	
	3	12.06	±0.4	12.37	±0.4	11.25	±0.4	12.16	±0.6	10.50		12.50	
	4	10.68	±0.13	11.18	±0.6	9.58	±0.45	11.41*	±0.55	9.25		11.60	
Serum IX—P.T.C. clotting time (sec.)	1	41.50	±2.0	43.62	±1.4	40.16	±1.8	42.00	±1.3	41.50		42.00	
	2	16.68	±0.6	19.12	±2.1	14.75	±1.0	18.20*	±1.4	14.50		21.60*	
	3	11.75	±0.5	12.06	±0.5	10.83	±0.7	12.05	±0.7	11.25		13.30	
	4	10.50	±0.4	11.06	±0.5	9.83	±0.5	11.47*	±0.55	10.25		12.00	
Plasma IX—P.T.C. clotting time (sec.)	1	48.18	±0.9	49.25	±1.2	52.33	±1.8	54.50	±1.7	52.00		52.30	
	2	22.31	±1.3	22.37*	±1.1	23.16	±1.2	23.83	±0.7	23.50		25.60	
	3	13.50	±0.5	13.62	±0.5	14.00	±0.7	13.91	±0.7	14.50		14.80	
	4	12.62	±0.5	12.80	±0.5	13.08	±0.6	13.33	±0.7	12.25		13.60	
Platelets Clotting time (sec.)	1	45.25	±3.4	48.87	±1.1	48.83	±1.2	47.76	±2.1	42.50		48.00	
	2	20.75	±1.1	21.12	±0.5	25.00	±1.5	19.60*	±1.1	20.50		18.60	
	3	15.93	±0.8	16.12	±0.5	16.58	±0.6	15.93	±0.7	17.50		15.00	
	4	15.25	±0.6	15.25*	±0.7	17.50	±0.5	15.68*	±0.55	17.25		14.60	

Group A: Patients with serum cholesterol below 250 mg. % (4).
Group B: Patients with serum cholesterol above 250 mg. % (3).
Group C: Myxedematous patient (1).

*Difference between "control" and "treated patients" is significant at $.01 < p \leq .05$.

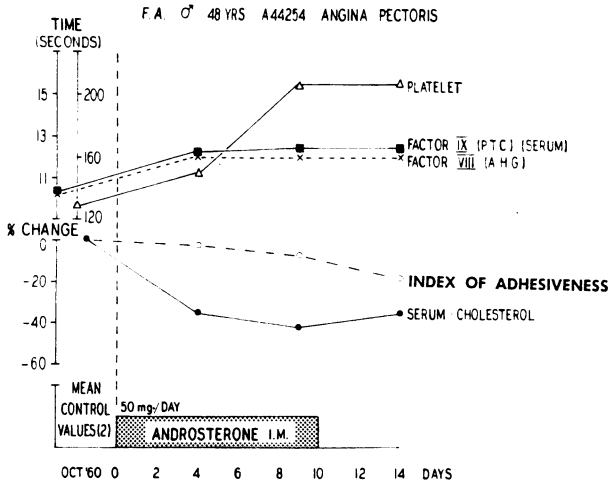

Fig. 4.—Effects of androsterone injected for 10 days at 50 mg./day to a patient suffering from angina pectoris on the same parameters as in Fig. 1. Note that the legend is the same as that in Fig. 1.

in platelet adhesive index, a prolongation in platelet clumping time, and an increase in thromboplastin generation test, are noted in Table VIII. The results obtained show the same trends as in patients receiving dextro-thyroxine. The changes obtained in a 71-year-old woman with myxedema are shown in Fig. 5. The laboratory findings in this woman were: a B.M.R. of −12; a radioactive iodine^{131} uptake after 24 hours of 4.9%, and a P.B.I. of 2.8 μg. %. The variations in the several tests are more marked than in the euthyroid patient and are shown in detail in Table IX.

TABLE VIII.—PATIENT F.A., A44254, 48 YEARS OLD

Tests	*Average control values (2)*	*During treatment mean values (3)*
Serum cholesterol	242 mg. %	168 mg. %
Platelet adhesive index	1.52	1.38
Platelet clumping time	127.5 sec.	190 sec.
At the fourth minute of incubation:		
(a) Activity of aluminum-treated plasma	10.25 sec.	12 sec.
(b) Activity of Factor IX (P.T.C.) (measured on serum)	10.25 sec.	12.1 sec.
(c) Activity of Factor IX (P.T.C.) (measured on plasma)	13.25 sec.	13.5 sec.
(d) Activity of platelets	19 sec.	16 sec.

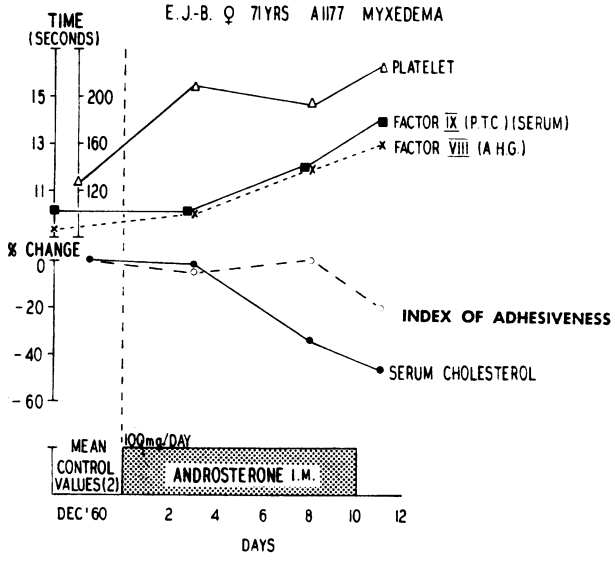

Fig. 5.—Effects of androsterone injected for 10 days at 100 mg./day to a patient with myxedema on the same parameters as in Fig. 1. Note that the legend is the same as that in Fig. 1.

TABLE IX.—PATIENT E.J.B., A1177, 71 YEARS OLD

Tests	*Average control values (2)*	*During treatment mean values (3)*
Serum cholesterol	520 mg. %	346 mg. %
Platelet adhesive index	1.3	1.19
Platelet clumping time	127.5 sec.	210 sec.
At the fourth minute of incubation:		
(a) Activity of aluminum-treated plasma	9.5 sec.	11.5 sec.
(b) Activity of Factor IX (P.T.C.) (measured on serum)	10.25 sec.	12 sec.
(c) Activity of Factor IX (P.T.C.) (measured on plasma)	12.25 sec.	13.5 sec.
(d) Activity of platelets	17 sec.	14.5 sec.

During androsterone administration, one patient developed a nonthrombocytopenic purpura on the fifth day of therapy.

DISCUSSION

These studies demonstrate a direct relationship between the fall in serum cholesterol and changes in factors involved in the first stage of the clotting mechanism during administration of dextro-thyroxine and androsterone to patients with atherosclerosis. The variations in blood coagulation consist of a prolongation of platelet clumping time, a decrease of platelet adhesive index, and an increase in plasma thromboplastin time.

The exact mechanism of this cholesterol-lowering effect is not completely understood, and must be approached on a speculative basis.[1, 23] Dextro-thyroxine has a great advantage over androsterone because it can be given orally, while androsterone must be given intramuscularly only. Dextro-thyroxine causes no side effects, while the site of injection of androsterone in aqueous suspension is very painful.

Our studies established a direct correlation between the atherosclerotic process and thrombotic tendencies which are the major causes of cardiovascular diseases and deaths at the present time. Whether the effects of dextro-thyroxine or androsterone on coagulation are due to the decrease in blood lipids or due to a direct action of the drug *per se* remains to be explained. It would be of great interest to study the changes in the plasma cephalins (phosphatidyl, ethanolamine and phosphatidyl serine) in atherosclerotic subjects receiving dextro-thyroxine or androsterone. Such a study is actually under way in our laboratory.

Androsterone administered intramuscularly definitely has a "thyromimetic" effect on cholesterol level and blood coagulation.

SUMMARY AND CONCLUSIONS

Thirty-one patients were studied; 23 received oral dextro-thyroxine and eight received intramuscular androsterone. The parameters which were investigated showed an over-all decrease of serum cholesterol and platelet adhesive index, a prolongation of platelet clumping time, a decrease in the activity of $Al(OH)_3$-treated plasma and factor IX on serum and plasma, and an acceleration of platelets in the thromboplastin generation test. Three myxedematous patients showed an increase of urinary androsterone and etiocholanolone with dextro-thyroxine therapy. The observed coincidence of the fall of serum cholesterol with the decrease in platelet adhesive index, the prolongation of platelet clumping time, and the increase in plasma thromboplastin time suggests a definite link between lipemia and clotting factors in the pathogenesis of thrombo-atherosclerosis.

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